UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,574	10/23/2000	Jean-Paul Behr	0652.2090000	9271

26111 7590 11/19/2002

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/555,574	Applicant(s) BEHR ET AL.	
	Examiner Mary M. Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,37-43,45,46 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,37-43,45,46 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-33, 37-43, 45-46 and 48 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for guanidyl-cysteine-decylamide ($C_{10}C^{G+}$) and ornithyl-cysteine-dodecylamide ($C_{12}CO$), and where the alkyl chain length is within functionally equivalent ranges, such as C_{14} and C_{16}) and methods of making and using said compositions in cells in culture and rodents, does not reasonably provide enablement for the scope of compositions claimed other than the guanidyl-cysteine-decylamide ($C_{10}C^{G+}$) and ornithyl-cysteine-dodecylamide ($C_{12}CO$) based compounds, nor methods of making and using said compositions in cells in any whole organism such as humans for therapeutic purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the Official Action mailed 03/27/02.

Claim **1** as amended is drawn to a <u>transfection</u> particle [for transfecting higher eukaryotic cells with nucleic acid molecules in vitro and in vivo] comprising one or more nucleic acid molecules condensed by organic cationic molecules, said particle being obtained by (1)

condensing said one or more nucleic acid molecules with identical or different organic cationic precursor molecules without crosslinking any of said one or more nucleic acid molecules, and (2) thereafter linking the precursor molecules to each other with one or more covalent bonds, wherein the linked precursor molecules remain [on the] condensed one or more nucleic acid molecules. Claim **2** specifies wherein the cationic molecules are lipids obtained by dimerization or oligomerization of cationic detergent precursor molecules. Claim **3** specifies wherein the cationic detergent precursor molecules comprise (a) at least one functional group for binding to one or more other detergent molecules, (b) at least one lipophilic residue, c) a non-toxic recipient backbone, (d) a cationic group for binding to nucleic acid molecules. Claim **4** specifies wherein the functional group of the cationic precursor detergent molecules for binding to other detergent molecules is a dimerizable or polymerizable functional group selected from the group consisting of thiols, acid hydrazides, aldehydes, amines, and ethylene residues that are suitably substituted to provide enamines upon reaction with an amine. Claim **5** specifies wherein the lipophilic residue is selected from the group consisting of lipophilic amides, esters and ethers. Claim **6** specifies wherein the functional group for binding to nucleic acid molecules is selected from an amine or derivative thereof. Claim **7** specifies wherein the functional group for binding to nucleic acid molecules is guanidine. Claims **8-11** specify wherein the organic cationic precursor molecule is represented by various compositions corresponding to the cited structures named general formula I. Claims **12-21** specify certain side groups for the compositions of general formula I in claims 8-11. Claim **22** specifies wherein the one or more covalent bonds between

the cationic molecules are degradable under [cellular] reductive or slightly acidic conditions, or in the presence of enzymes. Claims **23-26** specify wherein the transfection particle of claim 1 comprises a single nucleic acid molecule, such as a DNA, a DNA plasmid or an RNA. Claim **27** species that the particle of claim 1 is characterized in that it is linked via on e or more covalent bonds to one or more members of the group consisting of protein ligands, sugar residues, fusogenic peptides, viruses, adenoviruses, and combinations thereof [one or more cellular targeting functionalities and/or one or more functionalities capable of facilitating endocytosis]. Claim **28** further specifies wherein said [functionalities] one or more members of the group are linked via said one or more covalent bonds to the cationic molecules. Claim **29** specifies wherein said [functionalities] one or more members of the group are linked via said one or more covalent bonds to nucleic acid binding molecules that are present in addition to the cationic molecules. Claim **30** specifies wherein [the targeting functionality is a cellular] said one or more members of the group is a protein ligand. Claims **31-33** further specify wherein [the targeting functionality] said one or more members of the group is a sugar residue such as galactose or mannose. Claim **34** specifies that the transfection particle of claim 1 is characterized in that it carries one or more endosomolytic functions. Claim **35** specifies wherein said endosomolytic functions are linked to the cationic molecules. Claim **36** specifies wherein said functions are linked to nucleic acid binding molecules that are present in addition to the cationic molecules. Claim **37** specifies wherein said one or more members of the group [the endosomolytic function] is a fusogenic peptide. Claim **38** specifies wherein [the endosomolytic function] said one or

more members of the group is a virus. Claim **39** specifies wherein the virus is an adenovirus. New claim **48** is drawn to a transfection particle [for transfecting higher eukaryotic cells with nucleic acid molecules *in vitro* or *in vivo*] comprising: (a) one or more nucleic acid molecules; (b) identical or different organic cationic precursor molecules linked to each other via one or more covalent bonds; wherein said precursor molecules are ionically associated with said one or more nucleic acid molecules without forming any crosslinks between said nucleic acid molecules and said cationic precursor molecules, thereby condensing said one or more nucleic acid molecules.

Claim **40** is drawn to a method for preparing transfection particles of claim 1 wherein cationic precursor molecules are added to nucleic acid molecules in a suitable buffer, allowed to form complexes with the nucleic acid and allowed to covalently link to identical or different cationic precursor molecules on the nucleic acid template. Claim **41** specifies wherein the cationic precursor molecules are lipophilic and are allowed to covalently link under mild oxidative conditions.

Claims **42-43** are drawn to pharmaceutical compositions comprising a pharmaceutically effective amount of the transfection particle of claim 1, wherein the nucleic acid molecule is therapeutically active such as a plasmid encoding a therapeutically active protein. Claim **44** is drawn to a method for introducing therapeutically active nucleic acid into a mammal, wherein a transfection particle of claim 1 is administered to said mammal intradermally.

Claims **45-47** are drawn to kits comprising one or more nucleic acid molecules, one or more cationic precursor molecules, one or more cationic precursor molecules, suitable buffers, and other reagents or mechanical devices that are useful for preparation or purification [*in vitro* or *in vivo* application] of a transfection particle of claim 1; comprising in addition one or more members of the group consisting of nucleic acid binding molecules that are present in addition to the cationic molecules, protein ligands, sugar residues, fusogenic peptides, viruses, adenoviruses, and combinations thereof; comprising in addition or more functionality for cellular targeting; comprising in addition one or more endosomolytic functionalities.

Removal of the language from the claims specifically stating that the compositions are useful for both *"in vitro* or *in vivo"*, does not limit the claims further since they still broadly embrace use in both enviroments as amended. The claims thus retain the breath of function inside a cell either in culture or in a whole organism. The above functions are generic to all types of liposomes known in the art for administration of nucleic acids to cells in culture or in whole organisms, but the art teaches selective success of different types of liposomes for delivery of nucleic acids such as gene therapeutic agents. (Such art is discussed below.) The unpredictability in the art for design and use of *in vivo* therapeutic agents is maintained for the reasons stated in the previous office action.

The instant claims also retain important functional limitations regarding how the claimed liposomal compositions are made. Specifically, claims 40 and 41 teach formation of compositions having a covalent linkages between the cationic precursor molecules and the

nucleic acid template where the covalent linkage is allowed to form under mild oxidative conditions. It is this feature of the claimed compositions which is considered to distinguish Applicants' invention from the prior art, since other well-known liposomal compositions are necessarily represented as having covalent linkages between the cationic molecules linked to the nucleic acids. Claim 48 further provides the limitation wherein the cationic precursor molecules are linked to each other via one or more covalent bonds, but the precursor molecules are ionically associated with the nucleic acid molecules. The unpredictability in the art for the design of the broad scope of claimed compounds in view of such functional considerations in making the claimed compounds is maintained for the reasons set forth in the previous office action.

The specification as filed teaches making transfection particles having a di-sulfide bond formed between cysteine residues at the end of an alkyl chain where upon oxidation of the cysteine-alkyl precursor molecules and addition of the DNA template, the stable lipid/DNA particle is formed. The specification exemplifies this in Figure 1, Figure 3, and in the examples. Figure 10 shows that C8-Cys, C11-Cys and C12-Cys were not as effective as C10-Cys. The specification teaches on page 43 that the "oxidation of cysteine detergent $C_{10}C^{G+}$ into cystine lipid $(C_{10}C^{G+})_2$ occurs faster in the presence of template DNA." The specification further teaches by way of example complexing Spermine-N1, N12-bis-cysteineamide and calf-thymus DNA and teaches that "the SC_2 complexes and compacts DNA in the same manner as spermine. On the other hand, the formed particles seemed to be more stable vis a vis the ionic strength of the medium, which is in relation with the oxidation of the thiol functions." (Page 67) Figures 24-26

taught the effect of transferrin-polylysine on the delivery of $(C_{10}C^{G+})_2$/DNA complexes in cells in culture. Example 18 taught intradermal gene delivery of $(C_{10}C^{G+})_2$/ pCMVL DNA complexes in mice but no data on the therapeutic effects of such delivery. Example 20 taught transfection of BNL CL.2 cells with $(C_{12}CO)_2$/DNA complexes (ornithyl-cysteine-dodecylamide detergent as the starting material) for luciferase reporter gene expression.

While the specification as filed is enabling for making and using the exemplified types of liposomes for delivery of nucleic acids to cells in culture and in rodents, the specification is not enabled for making and using the breadth of claimed compositions for the functions claimed since neither the specification nor the art teach the predictability of substituting any type of precursor molecule with the scope of linkages claimed for administration of any type of nucleic acid especially for therapeutic uses to any whole organism as claimed.

As argued previously in the Official Action mailed 08/08/01, there is a high level of unpredictability for making and using transfection particles for successful achievement of transfection. See paragraph 2 in the Action which cites Zelphati et al. transfection particles known in the art for use in administering therapeutic nucleic acids to cells. While all the claimed limitations are art recognized molecules, their combination to form functional transfection particles does not carry an expectation of success absent specific guidance for the specific structures of precursor molecules, specific substitutions of linkages, etc., concentrations and ratios of concentrations, and the actual steps for formation of the claimed compositions. The closed prior art to the instant Cys-C10 compounds was taught by Staatz et al. (Liebigs Ann.

Chem. 1989: (a) pages 51-57 and (b) 127-131). They teach that "in order to synthesize a variable system of well-defined one- and two-chain chiral amphiphils that are able to form liposomes, we choose s-triazine as linking unit between the lipophilic and hydrophilic moieties. The lipophilic part is made of long-chain alcohols or alkylamines, whereas the hydrophilic part of the molecules is formed by the trifunctional amino acids L-cysteine, L-serine, or L-lysine. These are linked to the s-triazine with their w-functional group....On the investigation of their liposome-building properties only the cysteine amphiphiles with two alkyl chains are found to be capable of forming vesicles." (Abstract of (a)) Although they taught use of s-triazine in making their liposomes, they explicitly taught that the substitution of the precursor molecules did not function to form liposomes. As such, one of skill in the art would not have had an expectation of success to make and use any such transfection particle broadly claimed with any precursor molecule.

Schott et al. (Biochemica et Biophysica Acta 940, 1988, 127-135) further taught the design of palmitoyl derivatives of L-cysteine, cysteamine, L-cystine, cystamine and their incorporation into the bilayers of unilamellar liposomes. They provide specific guidance for the design of liposomes which specifically couple to antibodies but tech several general problems which are unpredictable in the liposome art. For instance on page 128 they teach that "the liposome-antibody complexes are still containing many non-used but activated sulfhydryl residues which are located on the outside as well as on the inner side of the bilayer membrane. When using such liposomes for cell-targeting it can not be excluded that these reactive liposomal groups may cause undesired side reactions. In regard to therapeutical application the possibility

of toxical side reactions has to be considered." They further teach that in design of liposomes the "size, homogeneity and stability" of the liposomes must be considered. (Page 128, col. A) On page 133 they taught other considerations of the design of liposomes: "In regard to a therapeutical application of derivatized liposomes we have first of all guaranteed that all components used for derivatization of the liposomes are non-toxic, analytically characterized and easily accessible. Another demand to be met is that the functionalized liposomes are obtained as small unilamellar vesicles in a reproducible population homogeneity (H) and hydrodynamic diameters (D) and can be stored over a longer period of time." They teach on page 134 the protection of the sulfhydryl residues for the storage of their liposomes in the presence of oxidizing agents to that dimerization won't occur. However, they also teach deprotection by reduction with dithiothreitol if needed. The teach calculation of the number of functional groups per liposome. They teach that "the stability of the liposomes is remarkable as sulfhydryl components not immobilized to liposomes lose their reactivity after some time at neutral pH." they teach practical considerations in the stearic design of such molecules. For example, "liposomes functionalized with phosphatidylethanolamide of carboxyacyl derivatives antibodies could only be coupled if the lipophilic part of the molecule was separated from the carboxylate function by a long spacer." They taught also practical considerations such as cost. "In regard to a therapeutic application (immunotargeting) the efficiency of liposomal loading with expensive antibodies should be as low as possible in order to avoid high costs and prevent unwanted immune reactions....The crucial point for in vivo experiments is that degradation of the

biodegradable antibody-liposome complexes in blood and serum proceeds slower than the cell targeting." They thus teach that the composition of the liposome, type of detergent, the concentration of materials, stearic hindrance, ability to form vesicles, number of binding regions, toxicity of the materials, degradation, ability to make (synthesize) a particular chemical design, addition of molecules for cell targeting, etc. are critical features which require experimentation in the art and testing in cells and whole organisms to determine. Due the myriad scope of possibilities in design of any transfecting particle having one or more covalent bonds, for the claimed functions and intended uses, delivery of nucleic acids, no general guidance is available absent experimentation for the characterization of any such potential compositions.

In regards to the use of any such liposomal composition for transportation of any nucleic acid for the intended uses of such transfection particles in vivo for therapeutic uses, there is a high level of unpredictability in the art for design of not only the transfecting agent, but the type of therapeutic DNA administered. Not every known type of transfection particle is suitable for transfection of any type of nucleic acid molecule. The design of the transfection molecule is thus intimately connected with the type of transfection nucleic acid administered and where the nucleic acid is administered. The instant invention contemplates improved delivery of nucleic acids by design of transfection agents which allow improved endosomolytic release of the nucleic acids, but no specific examples are given demonstrating how such a desired trait is designed into any type of transfection particle as instantly claimed. Furthermore, in regards to administration of any type of transfection particle to a whole organism, not every cell type is accessible equally

to administration of such transfection particles. Different cell types thus have different needs and considerations in design and delivery.

Freeman et al. is further cited to teach the considerations necessary in design of liposomes for gene therapy type uses for administration to a whole organism. They thought that at the time the invention was made "in summary, the results highlight some of the issues surrounding the preparation and dosing of DNA to the lungs but demonstrate that transfection can be achieved using DNA in conjunction with the appropriate additive. Along with efforts at the molecular and cellular level to enhance intracellular translocation of plasmid and increase protein copies, there are means whereby relatively simple formulations, that are readily scalable to manufacturing levels, can also improve transfection. The particular use of bile-salts, opens a new area of investigation and although their use in the lungs may be limited due to toxicity, their use with injectable preparations into tumors for example may be acceptable. More importantly, the results imply that other less toxic derivatives might be developed once a better understanding of the mechanisms of action are obtained." (Page 208) Although the use of bile-salts is not involved in the instant invention, the factors considered unpredictable by Freeman are the same. For instance, (1) routes of administration, (2) toxicity of the therapeutic agent, (3) effect amounts for therapeutic use, (4) understanding the mechanisms of action of the therapeutic compound in the whole organism remain to be highly unpredictable in the art of treatment of a whole organism. These facts directly relate to the design and use of liposomes for carrying therapeutic nucleic acids into whole organisms.

While the instant specification as filed contemplates specifically the design of ($C_{10}C^{G+}$) and ornithyl-cysteine-dodecylamide ($C_{12}CO$) liposomes and methods of making and using said compositions in cells in culture and in rodents, such results do not correlate to making any transfection particle broadly claimed for any use as claimed. One of skill in the art at the time of the invention was made would necessarily had to practice "trial and error" experimentation to make and use the scope of claimed transfection particles since neither the art nor the specification as filed provided sufficient guidance as to how to substitute any of the claimed limitations other than those exemplified in the specification in a particular concentration and order for the formation of liposomes that stability interact with nucleic acids for delivery into living cells and whole organisms. One of skill in the art would have necessarily practiced undue experimentation to make and use the various claimed compositions absent such guidance.

Response to Arguments

Applicant's arguments filed August 27, 2002, have been fully considered but they are not persuasive.

Applicant states on page 14 of the response that "[a]t least one critical feature which distinguishes the claims from the prior art also enables the full scope of those claims. In particular, the prior art does not anticipate, teach or suggest transfection particles comprising organic cationic precursor molecules *intermolecularly bonded* to other such molecules. Whereas such molecules in the claimed particles are covalently bonded to each other, they are only

ionically associated with the nucleic acid molecules. The claimed precursor molecules' capability of forming these intermolecular bonds is critical in facilitating the formation of applicants claimed transfection particles.... The intermolecular covalent bonds facilitate the formation of stable transfection particles."

Upon amending claims 15 and 17 to claim specific structures, the search of the art pointed to applicants' published work: Dauty et al. "Dimerizable Cationic Detergents with a Low cmc Condense Plasmid DNA into Nonometric Particles and Transfect Cells in Culture" from *Journal of the American Chemical Society*, Vol. 123, No. 38, Sept. 26, 2001, pp. 9227-9234; Dauty et al. "Intracellular Delivery of Nanometric DNA Particles via the Folate Receptor" from *Bioconjugate Chem.*, Vol. 13, 2002, pp. 831-839; Lleres et al., "DNA condensation by an oxidizable cationic detergent. Interactions with lipid vesicles." from *Chemistry and Physics of Lipids*, Vol. 111, 2001, pp. 59-71. None of these articles is prior art to the instant claims, but serves to further explain the types of molecules instantly claimed.

The Lleres et al. article discusses the benefits of the ornithinyl-cysteinyl-tetradecylamide able to convert itself via oxidative dimerization into a cationic cystine-lipid. (See Figure 1, page 61 for the chemical structures used: $C_{10}C^{G+}$, and C_{14}-CO) The Dauty et al. reference also taught that "a series of thiol detergents with various chain lengths (C_{12}-C-$_{16}$) and headgroups (ornithine or spermine) was prepared...." (see abstract). The method used was the "recently described ... general method for "freezing" such small DNA particles. It makes use of polymerizable α,ω-bisthiol oligocations or of dimerizable cationic thiol detergents for DNA condensation (Figure 1).

Subsequent oxidation to disulfides converts the reversible condensing agent into a polymer or a lipid, respectively. Stable particles formed with oligoamines or with oligolysines were eventually small but nonmonomolecular with respect to plasmid DNA. Solutions of particles resulting from the DNA-template-assisted dimerization of detergents into gemini surfactants, however, were remarkably homogeneous.... We therefore concentrated our efforts on the thiol amphiphiles. The short-chain cysteine-based detergents that were made initially proved to be poor transfection agents. Here, we describe a general synthesis of thiol-based dimerizable detergents that allowed us to explore several other headgroup and hydrocarbon combinations. Some derivatives exhibit both monomolecular plasmid DNA condensation *and* efficient cell transfection properties." (Page 9228) The article teaches further variability in the results on page 9229, Table 1, and use of the claimed headgroups on page 9232, Figure 7.

Thus while applicant is enabled for those molecules with demonstrated use as transfection particles, such as those shown in the Dauty et al. references, one of skill in the art would have maintained that applicant is not enabled for the breath of transfection particles instantly claimed. Applicants own work cites the unpredictability in the art among molecules useful in the "freezing" method, and shows the variability in results in Table 1 (page 9229). Applicant stated on page 9228 that only "[s]ome derivatives exhibit both monomolecular plasmid DNA condensation *and* efficient cell transfection properties." This is in view of the unpredictable factors such as size of particles, ability to interact with nucleic acids, and enter the cell for effective action therein.

Applicant states on page 16 of the response that "Applicants are not required to exhaustively provide experimental guidance for every potential transfection particle." Although applicant does not need only provide representative embodiments of the claimed constructs, the prior art did not provide any teaching of the guanidyl-cysteine-decylamide ($C_{10}C^{G+}$) and ornithyl-cysteine-dodecylamide ($C_{12}CO$)-type molecules, and the post art (applicants own work) states the factors considered unpredictable in the art for making these types of molecules. Claim 1 continues to read on a breath of compounds that have numerous possible R1 and/or R2 head groups. It is not clear from either the prior art or the specification as filed, how all the differently claimed substituted groups would functional equivalently to the disclosed and published head groups for use in applicant's method of "freezing". Applicant specifically states that molecules with thiol amphiphiles were much more successful that other types of head groups (Dauty et al., J. Chem. Soc., page 9228) in the disclosed methods.

Applicant states on page 18 of the response that "[t]he references cited by the Examiner do not support the enablement rejection. They are alleged to illustrate unpredictability in the state of the art. However, the references are irrelevant and inapplicable to assessing the predictability of Applicants' invention because they pertain to the predictability of forming liposomes instead of the claimed transfection particles. Moreover, the references' teachings actually support the enablement of Applicants' invention.... A liposome is a specific, ordered array of particular molecules, typically lipids. Lipophile-nucleic acid complexes can take a variety of physical forms and the claimed transfection particle is not required to have a liposomal

structure. Yet, these two terms, liposome and transfection particle, have been interchangeably used throughout the rejection...."

However, applicant's work, in the Lleres et al. article, states in the abstract that "[d]omains with a largest *molecular order* were obtained with dimeric C_{14}-CO/DNA complexes." The instantly claimed transfection particles are also ordered molecules with lipids. They are further used in the same way as liposomes, to deliver nucleic acids, such as vectors, to cells. Applicants' own work demonstrates the variabilities in function of the transfection particles in the same way the previously cited articles demonstrate the variabilities in making and using liposomes. Therefore, although applicant may distinguish the instant particles over the prior liposomal art based on the unique condensation method ("freezing" method) used, and the fact that applicants' molecules are smaller and "[l]aser light scattering and electron microscopy showed them to be made of individually condensed DNA molecules" (Dauty et al., J. Chem. Soc., page 9228, col. 1), the instantly claimed "transfection particles" have equivalent considerations for use in transfecting cells. In fact, as pointed out above, applicant points to the unpredictability in the art of use of any head group in the transfection particles, as well as the ability to transform cells (see page 9228 of the Dauty et al. J. Chem Soc. article). Furthermore, liposomes are also used as particles to transfect cells, and thus could be reasonable considered a transfecting particle.

Applicant further states on page 20 of the response that the previously cited references to use of SH bonds and oxidation as a mechanism for formation of liposomal compositions is

"irrelevant and inapplicable as Applicants' invention is directed to transfection particles and not liposomes." However, applicants' own work (Dauty et al., J. Chem. Soc., page 9228, col. 1) states for example that "[s]table particles formed with oligoamines or with oligolysines were eventually small but not monomolecular with respect to plasmid DNA... We therefore concentrated our efforts on the thiol amphiphiles...." This statement teaches that not all head groups will have an expectation of success to function in the disclosed methods of making the transfection particles, and thus there is unpredictability in the art for making the instant transfection particles for the breath of compositions claimed.

Applicants' arguments have not pointed out how the scope of exemplified molecules in the specification as filed enables the entire breath of compositions instantly claimed. For the closest prior art, the liposomal art, and the post-art of applicants' own work, there would appear to one skilled in the art that there remains a high level of unpredictability for making and using the entire breath of claimed compositions.

3. The claims are considered free of the prior art since the closest prior art is discussed above and does not specifically read on making cationic precursors with covalent bonds without crosslinking the lipid.

4. Applicant's amendment, to claim the specific compositions in claims 15 and 17, necessitated the application of new references having these compositions presented in this Office

action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
November 18, 2002

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600